```
# Simulates male mouse for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
# Uses scaled metabolism constants from Yang et al. 2012 Table 3


#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))


#Load libraries needed to run scenario
library(deSolve)

#Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

# Physiolgical parameters path
#Load the parameters
source('./params/Male_Mouse_3.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6     #hours per day to expose
ddaysperwk <- 5  #days of week to expose
dexpend <- 5     #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<-  12.3

ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
```

```
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <-  cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode",atol=1.0e-10,
rtol=1.0e-8,
              dllname = mName, initforc="initforc", forcings=forcings, initfunc =
"initmod", nout = length(Outputs),
              fcontrol=list(method="linear"), outnames = Outputs)

  }
  outlist[[i]] <- out[33601,]
}
frout1 <- data.frame(outlist)
dout <- data.frame(t(frout1), row.names=paste(1:3))
rout <- cbind(dout[,c(21,22,23,24)])

"Male Mouse Table 3"
rout


#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

```
#Simulates male mouse for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
#Uses metabolism constants from revised optimization using fixed Km

#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))


#Load libraries needed to run scenario
library(deSolve)

#Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiolgical parameters path
#Load the parameters
source('./params/Male_Mouse_5.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6     #hours per day to expose
ddaysperwk <- 5  #days of week to expose
dexpend <- 5     #days of exposure
parms["TSTOP"] <- tstop

# Source forcing functions
# This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<-  12.3

ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
ppm2 <- list()
```

```
for(i in 1:nrow(cinh1)){

  parms["CONC"] <-  cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10,
rtol=1.0e-8,
              dllname = mName, initforc="initforc", forcings=forcings, initfunc =
"initmod", nout = length(Outputs),
              fcontrol=list(method="linear"), outnames = Outputs)

  }
  outlist[[i]] <- out[33601,]
}
frout1 <- data.frame(outlist)
dout <- data.frame(t(frout1), row.names=paste(1:3))
rout <- cbind(dout[,c(21,22,23,24)])

"Male Mouse Reoptimized Values with Km for Lung and Kidney Fixed to Liver Km"
rout


#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

```
#Simulates male rat for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
#Uses metabolism constants from Yang et al. 2012 Table 2

#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))


#Load libraries needed to run scenario
library(deSolve)

#Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiolgical parameters path
#Load the parameters
source('./params/Male_Rat_2.R')
source('./states.R')

# timing variables for forcing functions
dstart <- tstart
dlength <- 6     #hours per day to expose
ddaysperwk <- 5  #days of week to expose
dexpend <- 5     #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<-  12.3


ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
```

```
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <-  cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10,
rtol=1.0e-8,
              dllname = mName, initforc="initforc", forcings=forcings, initfunc =
"initmod", nout = length(Outputs),
              fcontrol=list(method="linear"), outnames = Outputs)

  }
  outlist[[i]] <- out[33601,]
}
frout1 <- data.frame(outlist)
dout <- data.frame(t(frout1), row.names=paste(1:3))
rout <- cbind(dout[,c(21,22,23,24)])

"Male Rat Table 2"
rout



#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

```
# Simulates male rat for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
# Uses scaled metabolism constants from Yang et al. 2012 Table 3


#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))


#Load libraries needed to run scenario
library(deSolve)

#Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiolgical parameters path
#Load the parameters
source('./params/Male_Rat_3.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6     #hours per day to expose
ddaysperwk <- 5  #days of week to expose
dexpend <- 5     #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<-  12.3


ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
```

```
outlist <- list()
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <-  cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10,
rtol=1.0e-8,
              dllname = mName, initforc="initforc", forcings=forcings, initfunc =
"initmod", nout = length(Outputs),
              fcontrol=list(method="linear"), outnames = Outputs)

  }
  outlist[[i]] <- out[33601,]
}
frout1 <- data.frame(outlist)
dout <- data.frame(t(frout1), row.names=paste(1:3))
rout <- cbind(dout[,c(21,22,23,24)])

"Male Rat Table 3"
rout



#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

```
#Simulates male rat for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
#Uses metabolism constants from revised optimization using fixed Km

#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))


#Load libraries needed to run scenario
library(deSolve)

#Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiolgical parameters path

#Load the parameters
source('./params/Male_Rat_5.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6     #hours per day to expose
ddaysperwk <- 5  #days of week to expose
dexpend <- 5     #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<-  12.3


ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
```

```
outlist <- list()
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <-  cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10,
rtol=1.0e-8,
              dllname = mName, initforc="initforc", forcings=forcings, initfunc =
"initmod", nout = length(Outputs),
              fcontrol=list(method="linear"), outnames = Outputs)

  }
  outlist[[i]] <- out[33601,]
}
frout1 <- data.frame(outlist)
dout <- data.frame(t(frout1), row.names=paste(1:3))
rout <- cbind(dout[,c(21,22,23,24)])

"Male Rat Reoptimized Values with Km for Lung and Kidney Fixed to Liver Km"
rout



#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

#13 ppm mouse in vivo study - 15 day exposure (last day is nose-only),
time,cart
0.5,0.97
0.5,0.82
0.5,1.12
0.5,1.22
3,0.6
3,2.7
3,2.03
3,2.1
3,2.24
6,2.08
6,1.75
6,1.53
6,1.37
6,1.16
6.083,0.08
6.083,0.09
6.083,0.16
6.17,0.1
6.17,0.25
102,0.17
102,0.23
102,0.2
102,0.18
438,0.28
438,0.33
438,0.24
438,0.31

#32 ppm mouse in vivo study - 15 day exposure (last day is nose-only),
time,cart
0.5,3
0.5,2.27
0.5,1.66
0.5,2.08
0.5,0.69
3,3.94
3,3.9
3,1.52
3,2.48
3,1.68
3,3.87
6,2.26
6,1.26
6,4.18
6,2.06
6.083,0.46
6.083,0.41
6.083,0.92
6.083,0.52
6.083,0.77
6.17,0.28
6.17,0.26
6.17,0.1
6.17,0.12
6.17,0.13
6.25,0.18
6.25,0.31
6.25,0.69
6.25,0.16
6.25,0.13
102,2.32
102,2.26
102,1.15
102,1.32
102,0.88
438,0.75
438,2.08
438,1.6
438,1.12
438,1.45

#32 ppm mouse in vivo study - 15 day exposure (last day is nose-only),
time,cart
0.5,5.92
0.5,4.86
0.5,4.82
0.5,8.26
0.5,7.69
3,7.42
3,12.95
3,7.18
3,3.46
3,5.62
6,9
6,6.46
6,7.63
6,8.79
6,8.12
6.083,1.39
6.083,3.01
6.083,1.62
6.083,0.92
6.083,1.59
6.17,0.66
6.17,1.46
6.17,0.67
6.17,0.88
6.17,0.93
6.25,0.94
6.25,0.63
6.25,0.57
6.25,0.64
6.25,0.58
102,3.73
102,5.48
102,4.09
102,3
102,6.43
438,4.44
438,3.64
438,2.76
438,3.41
438,1.96

```
setwd(dirname(parent.frame(2)$ofile))

# set the name of your model
mName <- "chloroprene.model"

#Remove old model files before building model
#ensures files are reset with changes in model
file.remove(paste(mName, ".c", sep = ""))
file.remove(paste(mName, ".o", sep = ""))
file.remove(paste(mName, ".dll", sep = ""))
file.remove(paste(mName, "_inits.R", sep = ""))

#command to unload dll file (need if rebuilding dll file)
#dyn.unload(paste0(mPath,mName,.Platform$dynlib.ext))

system(paste("../mod/mod.exe -R ", mName, " ", mName, ".c", sep = ""))

system(paste0("R CMD SHLIB ", mName, ".c", sep = ""))
```

```
#Initial state values

Y <- c(
  AI = 0.0,
  AX = 0.0,
  AM = 0.0,
  AMLU = 0.0,
  AMK = 0.0,
  ALU = 0.0,
  AL = 0.0,
  AK = 0.0,
  AS = 0.0,
  AR = 0.0,
  AF = 0.0
)
```

```
#Female mouse paramters (Table 2 Yang et al. 2012)
#Metabolism is based on posterior values from
#MCMC analysis of the female mouse in vitro data

parms <-c(
BW = 0.03 ,      # Body weight
QPC = 30. ,      # Unscaled Alveolar Vent
QCC = 30. ,      # Unscaled Cardiac Output

#FRACTIONAL BLOOD FLOWS TO TISSUES
QLC = 0.161 ,    # Flow to Liver as % Cardiac Output
QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
QSC = 0.15  ,    # Flow to Slow as % Cardiac Output
QKC = 0.09  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

#FRACTIONAL VOLUMES OF TISSUES
VLC = 0.055 ,    # Volume Liver as % Body Weight
VLUC = 0.007 ,    # Volume Lung as % Body Weight
VFC = 0.1   ,    # Volume Fat as % Body Weight
VRC = 0.08098 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.384  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0167 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)

#PARTITION COEFFICIENTS PARENT
PL = 1.25 ,     # Liver/Blood Partition Coefficient
PLU = 2.38 ,     # Lung/Blood Partition Coefficient
PF = 17.29 ,     # Fat/Blood Partition Coefficient
PS = 0.58  ,    # Slow/Blood Partition Coefficient
PR = 1.76 ,     # Rapid/Blood Partition Coefficient
PB = 7.83 ,     # Blood/Air Partition Coefficient
PK = 1.76 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
# Metabolism in Liver
VMAXC = 8.88  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.08  ,  # Km for Oxidative Pathway:Liver
# Metabolism in Lung
VMAXCLU = 0.11,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.25  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
# Metabolism in Kidney (YYang 2009)
VMAXCKid = 0.03 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 9.59  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0      # Initial concentration (ppm)
```

)

```
#Female mouse paramters (Table 3 Yang et al. 2012)
#Metabolism is based on deterministic estimates with Nelder-Mead algorithem


parms <-c(
BW = 0.03 ,      # Body weight
QPC = 30. ,      # Unscaled Alveolar Vent
QCC = 30. ,      # Unscaled Cardiac Output

#FRACTIONAL BLOOD FLOWS TO TISSUES
QLC = 0.161 ,    # Flow to Liver as % Cardiac Output
QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
QSC = 0.15  ,    # Flow to Slow as % Cardiac Output
QKC = 0.09  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

#FRACTIONAL VOLUMES OF TISSUES
VLC = 0.055 ,    # Volume Liver as % Body Weight
VLUC = 0.007 ,    # Volume Lung as % Body Weight
VFC = 0.1  ,    # Volume Fat as % Body Weight
VRC = 0.08098 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.384  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0167 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)

#PARTITION COEFFICIENTS PARENT
PL = 1.25 ,     # Liver/Blood Partition Coefficient
PLU = 2.38 ,     # Lung/Blood Partition Coefficient
PF = 17.29 ,     # Fat/Blood Partition Coefficient
PS = 0.58  ,    # Slow/Blood Partition Coefficient
PR = 1.76 ,     # Rapid/Blood Partition Coefficient
PB = 7.83 ,     # Blood/Air Partition Coefficient
PK = 1.76 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
# Metabolism in Liver
VMAXC = 6.3863  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.0469  ,  # Km for Oxidative Pathway:Liver
# Metabolism in Lung
VMAXCLU = 0.1486,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.246  ,    # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,    # Pseudo-first order clearance in lung (Km unidentifiable)
# Metabolism in Kidney (YYang 2009)
VMAXCKid = 0.0003 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.1505  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0      # Initial concentration (ppm)
```

)

```
#Female mouse paramters (Re-estimated CVL 2017)
#Metabolism is based on deterministic estimates from Nelder-Mead algorithm
#Km was fixed to average of male and female mouse liver km


parms <-c(
BW = 0.03 ,      # Body weight
QPC = 30. ,      # Unscaled Alveolar Vent
QCC = 30. ,      # Unscaled Cardiac Output

#FRACTIONAL BLOOD FLOWS TO TISSUES
QLC = 0.161 ,    # Flow to Liver as % Cardiac Output
QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
QSC = 0.15  ,    # Flow to Slow as % Cardiac Output
QKC = 0.09  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

#FRACTIONAL VOLUMES OF TISSUES
VLC = 0.055 ,    # Volume Liver as % Body Weight
VLUC = 0.007 ,    # Volume Lung as % Body Weight
VFC = 0.1  ,    # Volume Fat as % Body Weight
VRC = 0.08098 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.384  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0167 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)

#PARTITION COEFFICIENTS PARENT
PL = 1.25 ,     # Liver/Blood Partition Coefficient
PLU = 2.38 ,     # Lung/Blood Partition Coefficient
PF = 17.29 ,     # Fat/Blood Partition Coefficient
PS = 0.58  ,    # Slow/Blood Partition Coefficient
PR = 1.76 ,     # Rapid/Blood Partition Coefficient
PB = 7.83 ,     # Blood/Air Partition Coefficient
PK = 1.76 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
# Metabolism in Liver
VMAXC = 8.5150  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.0841  ,  # Km for Oxidative Pathway:Liver
# Metabolism in Lung
VMAXCLU = 0.0594,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.0841  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
# Metabolism in Kidney (YYang 2009)
VMAXCKid = 0.0007 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.0841  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
```

```
CONC = 0.0      # Initial concentration (ppm)
)
```

```
#Female rat paramters (Table 2 Yang et al. 2012)
#Metabolism is based on posterior values from
#MCMC analysis of the female rat in vitro data
#Female Fischer Rat

parms <-c(
  BW = 0.25 ,     # Body weight
  QPC = 21. ,     # Unscaled Alveolar Vent
  QCC = 18. ,     # Unscaled Cardiac Output

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.183 ,   # Flow to Liver as % Cardiac Output
  QFC = 0.07  ,   # Flow to Fat as % Cardiac Output
  QSC = 0.278  ,   # Flow to Slow as % Cardiac Output
  QKC = 0.14  ,   # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.0366 ,   # Volume Liver as % Body Weight
  VLUC = 0.005 ,   # Volume Lung as % Body Weight
  VFC = 0.1  ,   # Volume Fat as % Body Weight
  VRC = 0.04644 ,   # Volume Rapid Perfused as % Body Weight
  VSC = 0.4  ,   # Volume Slow Perfused as % Body Weight
  VKC = 0.0073 ,   # Volume Kidney as % Body Weight (Brown et. al. 1997)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.57 ,    # Liver/Blood Partition Coefficient
  PLU = 1.84 ,    # Lung/Blood Partition Coefficient
  PF = 16.87 ,    # Fat/Blood Partition Coefficient
  PS = 0.60  ,   # Slow/Blood Partition Coefficient
  PR = 2.27 ,    # Rapid/Blood Partition Coefficient
  PB = 7.35 ,    # Blood/Air Partition Coefficient
  PK = 2.27 ,    # Kidney/Blood Partition Coefficient

  #KINETIC CONSTANTS
  MW = 88.5  , # Molecular weight (g/mol)
  # Metabolism in Liver
  VMAXC = 9.37  , # Scaled VMax for Oxidative Pathway:Liver
  KM = 0.09  ,  # Km for Oxidative Pathway:Liver
  # Metabolism in Lung
  VMAXCLU = 0.0  ,  # Scaled VMax for Oxidative Pathway:Lung
  KMLU = 0.25  ,   # Km for Oxidative Pathway:Lung
  KFLUC = 0.16  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
  # Metabolism in Kidney (YYang 2009)
  VMAXCKid = 0.02 , # Scaled VMax for Oxidative Pathway:Kidney
  KMKD = 0.05  ,  # Km for Oxidative Pathway :Kidney

  #DOSING INFORMATION
  TSTOP = 7.0 ,
```

```
  CONC = 0.0      # Initial concentration (ppm)
)
```

```
#Female rat paramters (Table 3 Yang et al. 2012)
#Metabolism is based on deterministic estimates with Nelder-Mead algorithem
#Female Fischer Rat

parms <-c(
  BW = 0.25 ,      # Body weight
  QPC = 21. ,      # Unscaled Alveolar Vent
  QCC = 18. ,      # Unscaled Cardiac Output

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.183 ,    # Flow to Liver as % Cardiac Output
  QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
  QSC = 0.278  ,    # Flow to Slow as % Cardiac Output
  QKC = 0.14  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.0366 ,    # Volume Liver as % Body Weight
  VLUC = 0.005 ,    # Volume Lung as % Body Weight
  VFC = 0.1  ,    # Volume Fat as % Body Weight
  VRC = 0.04644 ,    # Volume Rapid Perfused as % Body Weight
  VSC = 0.4  ,    # Volume Slow Perfused as % Body Weight
  VKC = 0.0073 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.57 ,     # Liver/Blood Partition Coefficient
  PLU = 1.84 ,     # Lung/Blood Partition Coefficient
  PF = 16.87 ,     # Fat/Blood Partition Coefficient
  PS = 0.60  ,    # Slow/Blood Partition Coefficient
  PR = 2.27 ,     # Rapid/Blood Partition Coefficient
  PB = 7.35 ,     # Blood/Air Partition Coefficient
  PK = 2.27 ,     # Kidney/Blood Partition Coefficient

  #KINETIC CONSTANTS
  MW = 88.5  , # Molecular weight (g/mol)
  # Metabolism in Liver
  VMAXC = 7.0647  , # Scaled VMax for Oxidative Pathway:Liver
  KM = 0.0726  ,  # Km for Oxidative Pathway:Liver
  # Metabolism in Lung
  VMAXCLU = 0.0  ,  # Scaled VMax for Oxidative Pathway:Lung
  KMLU = 0.0885  ,   # Km for Oxidative Pathway:Lung
  KFLUC = 0.138  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
  # Metabolism in Kidney (YYang 2009)
  VMAXCKid = 0.0087 , # Scaled VMax for Oxidative Pathway:Kidney
  KMKD = 0.0327  ,  # Km for Oxidative Pathway :Kidney

  #DOSING INFORMATION
  TSTOP = 7.0 ,
  CONC = 0.0      # Initial concentration (ppm)
```

)

```
#Female rat paramters (Re-estimated CVL 2017)
#Metabolism is based on deterministic estimates from Nelder-Mead algorithm
#Km was fixed to average of male and female rat liver km
#Female Fischer Rat

parms <-c(
  BW = 0.25 ,     # Body weight
  QPC = 21. ,     # Unscaled Alveolar Vent
  QCC = 18. ,     # Unscaled Cardiac Output

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.183 ,   # Flow to Liver as % Cardiac Output
  QFC = 0.07  ,   # Flow to Fat as % Cardiac Output
  QSC = 0.278  ,   # Flow to Slow as % Cardiac Output
  QKC = 0.14  ,   # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.0366 ,   # Volume Liver as % Body Weight
  VLUC = 0.005 ,   # Volume Lung as % Body Weight
  VFC = 0.1  ,   # Volume Fat as % Body Weight
  VRC = 0.04644 ,   # Volume Rapid Perfused as % Body Weight
  VSC = 0.4  ,   # Volume Slow Perfused as % Body Weight
  VKC = 0.0073 ,   # Volume Kidney as % Body Weight (Brown et. al. 1997)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.57 ,    # Liver/Blood Partition Coefficient
  PLU = 1.84 ,    # Lung/Blood Partition Coefficient
  PF = 16.87 ,    # Fat/Blood Partition Coefficient
  PS = 0.60  ,   # Slow/Blood Partition Coefficient
  PR = 2.27 ,    # Rapid/Blood Partition Coefficient
  PB = 7.35 ,    # Blood/Air Partition Coefficient
  PK = 2.27 ,    # Kidney/Blood Partition Coefficient

  #KINETIC CONSTANTS
  MW = 88.5  , # Molecular weight (g/mol)
  # Metabolism in Liver
  VMAXC = 5.7141  , # Scaled VMax for Oxidative Pathway:Liver
  KM = 0.0611  ,  # Km for Oxidative Pathway:Liver
  # Metabolism in Lung
  VMAXCLU = 0.0060  ,  # Scaled VMax for Oxidative Pathway:Lung
  KMLU = 0.0611  ,   # Km for Oxidative Pathway:Lung
  KFLUC = 0.0  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
  # Metabolism in Kidney (YYang 2009)
  VMAXCKid = 0.0133 , # Scaled VMax for Oxidative Pathway:Kidney
  KMKD = 0.0611  ,  # Km for Oxidative Pathway :Kidney

  #DOSING INFORMATION
  TSTOP = 7.0 ,
```

```
  CONC = 0.0      # Initial concentration (ppm)
)
```

```
#Human paramters (Table 2 Yang et al. 2012)
#Metabolism is based on posterior values from
#MCMC analysis of the human in vitro data

parms <-c(
BW = 70.0 ,      # Body weight
QPC = 27.75 ,      # Unscaled Alveolar Vent
QCC = 12.89 ,      # Unscaled Cardiac Output
QLC = 0.227 ,    # Flow to Liver as % Cardiac Output
QFC = 0.052  ,    # Flow to Fat as % Cardiac Output
QSC = 0.191  ,    # Flow to Slow as % Cardiac Output
QKC = 0.175  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)
VLC = 0.0257 ,    # Volume Liver as % Body Weight
VLUC = 0.008 ,    # Volume Lung as % Body Weight
VFC = 0.27  ,    # Volume Fat as % Body Weight
VRC = 0.0533 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.4  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0044 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)
PL = 1.44 ,     # Liver/Blood Partition Coefficient
PLU = 2.92 ,     # Lung/Blood Partition Coefficient
PF = 28.38 ,     # Fat/Blood Partition Coefficient
PS = 0.99  ,    # Slow/Blood Partition Coefficient
PR = 2.64 ,     # Rapid/Blood Partition Coefficient
PB = 4.54 ,     # Blood/Air Partition Coefficient
PK = 2.64 ,     # Kidney/Blood Partition Coefficient
MW = 88.5  , # Molecular weight (g/mol)
VMAXC = 20.4  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.04  ,  # Km for Oxidative Pathway:Liver
VMAXCLU = 0.0,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.25  ,    # Km for Oxidative Pathway:Lung
KFLUC = 0.05  ,    # Pseudo-first order clearance in lung (Km unidentifiable)
VMAXCKid = 0.0 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 9.59  ,  # Km for Oxidative Pathway :Kidney
TSTOP = 7.0 ,
CONC = 0.0      # Initial concentration (ppm)
)
```

```
#Human paramters (Table 3 Yang et al. 2012)
#Metabolism is based on deterministic estimates with Nelder-Mead algorithem

parms <-c(
BW = 70.0 ,     # Body weight
QPC = 27.75 ,     # Unscaled Alveolar Vent
QCC = 12.89 ,     # Unscaled Cardiac Output
QLC = 0.227 ,   # Flow to Liver as % Cardiac Output
QFC = 0.052  ,   # Flow to Fat as % Cardiac Output
QSC = 0.191  ,   # Flow to Slow as % Cardiac Output
QKC = 0.175  ,   # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)
VLC = 0.0257 ,   # Volume Liver as % Body Weight
VLUC = 0.008 ,   # Volume Lung as % Body Weight
VFC = 0.27  ,   # Volume Fat as % Body Weight
VRC = 0.0533 ,   # Volume Rapid Perfused as % Body Weight
VSC = 0.4  ,   # Volume Slow Perfused as % Body Weight
VKC = 0.0044 ,   # Volume Kidney as % Body Weight (Brown et. al. 1997)
PL = 1.44 ,    # Liver/Blood Partition Coefficient
PLU = 2.92 ,    # Lung/Blood Partition Coefficient
PF = 28.38 ,    # Fat/Blood Partition Coefficient
PS = 0.99  ,   # Slow/Blood Partition Coefficient
PR = 2.64 ,    # Rapid/Blood Partition Coefficient
PB = 4.54 ,    # Blood/Air Partition Coefficient
PK = 2.64 ,    # Kidney/Blood Partition Coefficient
MW = 88.5  , # Molecular weight (g/mol)
VMAXC = 20.2317  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.0398  ,  # Km for Oxidative Pathway:Liver
VMAXCLU = 0.0,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.0885  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.1656  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
VMAXCKid = 0.0 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.0885  ,  # Km for Oxidative Pathway :Kidney
TSTOP = 7.0 ,
CONC = 0.0     # Initial concentration (ppm)
)
```

```
#Human paramters (Re-estimated CVL 2017)
#Metabolism is based on deterministic estimates from Nelder-Mead algorithm
#Km was fixed to human liver km


parms <-c(
BW = 70.0 ,      # Body weight
QPC = 27.75 ,      # Unscaled Alveolar Vent
QCC = 12.89 ,      # Unscaled Cardiac Output
QLC = 0.227 ,    # Flow to Liver as % Cardiac Output
QFC = 0.052  ,    # Flow to Fat as % Cardiac Output
QSC = 0.191  ,    # Flow to Slow as % Cardiac Output
QKC = 0.175  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)
VLC = 0.0257 ,    # Volume Liver as % Body Weight
VLUC = 0.008 ,    # Volume Lung as % Body Weight
VFC = 0.27  ,    # Volume Fat as % Body Weight
VRC = 0.0533 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.4  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0044 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)
PL = 1.44 ,     # Liver/Blood Partition Coefficient
PLU = 2.92 ,     # Lung/Blood Partition Coefficient
PF = 28.38 ,     # Fat/Blood Partition Coefficient
PS = 0.99  ,    # Slow/Blood Partition Coefficient
PR = 2.64 ,     # Rapid/Blood Partition Coefficient
PB = 4.54 ,     # Blood/Air Partition Coefficient
PK = 2.64 ,     # Kidney/Blood Partition Coefficient
MW = 88.5  , # Molecular weight (g/mol)
VMAXC = 20.2317 , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.0398  ,  # Km for Oxidative Pathway:Liver
VMAXCLU = 0.0191,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.0398  ,    # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,    # Pseudo-first order clearance in lung (Km unidentifiable)
VMAXCKid = 0.0 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.0398  ,  # Km for Oxidative Pathway :Kidney
TSTOP = 7.0 ,
CONC = 0.0      # Initial concentration (ppm)
)
```

```
#Male mouse paramters (Table 2 Yang et al. 2012)
#Metabolism is based on posterior values from
#MCMC analysis of the male mouse in vitro data

parms <-c(
  BW = 0.03 ,      # Body weight
  QPC = 30. ,      # Unscaled Alveolar Vent
  QCC = 30. ,      # Unscaled Cardiac Output

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.161 ,    # Flow to Liver as % Cardiac Output
  QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
  QSC = 0.15  ,    # Flow to Slow as % Cardiac Output
  QKC = 0.09  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.055 ,    # Volume Liver as % Body Weight
  VLUC = 0.007 ,    # Volume Lung as % Body Weight
  VFC = 0.1  ,    # Volume Fat as % Body Weight
  VRC = 0.08098 ,    # Volume Rapid Perfused as % Body Weight
  VSC = 0.384  ,    # Volume Slow Perfused as % Body Weight
  VKC = 0.0167 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.25 ,     # Liver/Blood Partition Coefficient
  PLU = 2.38 ,     # Lung/Blood Partition Coefficient
  PF = 17.3 ,     # Fat/Blood Partition Coefficient
  PS = 0.58  ,    # Slow/Blood Partition Coefficient
  PR = 1.76 ,     # Rapid/Blood Partition Coefficient
  PB = 7.83 ,     # Blood/Air Partition Coefficient
  PK = 1.76 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
# Metabolism in Liver
VMAXC = 18.54  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.12  ,  # Km for Oxidative Pathway:Liver
# Metabolism in Lung
VMAXCLU = 0.60  ,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.20  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
# Metabolism in Kidney (YYang 2009)
VMAXCKid = 0.08 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.068  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0     # Initial concentration (ppm)
```

)

```
#Male mouse paramters (Table 3 Yang et al. 2012)
#Metabolism is based on deterministic estimates with Nelder-Mead algorithem


parms <-c(
  BW = 0.03 ,      # Body weight
  QPC = 30. ,      # Unscaled Alveolar Vent
  QCC = 30. ,      # Unscaled Cardiac Output

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.161 ,    # Flow to Liver as % Cardiac Output
  QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
  QSC = 0.15  ,    # Flow to Slow as % Cardiac Output
  QKC = 0.09  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.055 ,    # Volume Liver as % Body Weight
  VLUC = 0.007 ,    # Volume Lung as % Body Weight
  VFC = 0.1  ,    # Volume Fat as % Body Weight
  VRC = 0.08098 ,    # Volume Rapid Perfused as % Body Weight
  VSC = 0.384  ,    # Volume Slow Perfused as % Body Weight
  VKC = 0.0167 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.25 ,     # Liver/Blood Partition Coefficient
  PLU = 2.38 ,     # Lung/Blood Partition Coefficient
  PF = 17.3 ,     # Fat/Blood Partition Coefficient
  PS = 0.58  ,    # Slow/Blood Partition Coefficient
  PR = 1.76 ,     # Rapid/Blood Partition Coefficient
  PB = 7.83 ,     # Blood/Air Partition Coefficient
  PK = 1.76 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
# Metabolism in Liver
VMAXC = 18.4492  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.1204  ,  # Km for Oxidative Pathway:Liver
# Metabolism in Lung
VMAXCLU = 0.7726  ,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.1770  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
# Metabolism in Kidney (YYang 2009)
VMAXCKid = 0.0716 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.0443  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0     # Initial concentration (ppm)
```

)

```
#Male mouse paramters (Re-estimated CVL 2017)
#Metabolism is based on deterministic estimates from Nelder-Mead algorithm
#Km was fixed to average of male and female mouse liver km

parms <-c(
  BW = 0.03 ,      # Body weight
  QPC = 30. ,      # Unscaled Alveolar Vent
  QCC = 30. ,      # Unscaled Cardiac Output

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.161 ,    # Flow to Liver as % Cardiac Output
  QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
  QSC = 0.15  ,    # Flow to Slow as % Cardiac Output
  QKC = 0.09  ,    # Flow to Kidney as % Cardiac Output (Brown et. al. 1997)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.055 ,    # Volume Liver as % Body Weight
  VLUC = 0.007 ,    # Volume Lung as % Body Weight
  VFC = 0.1  ,    # Volume Fat as % Body Weight
  VRC = 0.08098 ,    # Volume Rapid Perfused as % Body Weight
  VSC = 0.384  ,    # Volume Slow Perfused as % Body Weight
  VKC = 0.0167 ,    # Volume Kidney as % Body Weight (Brown et. al. 1997)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.25 ,     # Liver/Blood Partition Coefficient
  PLU = 2.38 ,     # Lung/Blood Partition Coefficient
  PF = 17.3 ,     # Fat/Blood Partition Coefficient
  PS = 0.58  ,    # Slow/Blood Partition Coefficient
  PR = 1.76 ,     # Rapid/Blood Partition Coefficient
  PB = 7.83 ,     # Blood/Air Partition Coefficient
  PK = 1.76 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
# Metabolism in Liver
VMAXC = 14.9013  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.0841  ,  # Km for Oxidative Pathway:Liver
# Metabolism in Lung
VMAXCLU = 0.2972  ,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.0841  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
# Metabolism in Kidney (YYang 2009)
VMAXCKid = 0.0716 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.0841  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0     # Initial concentration (ppm)
```

)

```
#Male rat paramters (Table 2 Yang et al. 2012)
#Metabolism is based on posterior values from
#MCMC analysis of the male rat in vitro data
#Male Fischer Rat

parms <-c(
BW = 0.25 ,      # Body weight
QPC = 21. ,      # Unscaled Alveolar Vent
QCC = 18. ,      # Unscaled Cardiac Output

#FRACTIONAL BLOOD FLOWS TO TISSUES
QLC = 0.183 ,    # Flow to Liver as % Cardiac Output
QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
QSC = 0.278  ,    # Flow to Slow as % Cardiac Output
QKC = 0.14  ,    # Flow to Kidney as % Cardiac Output

#FRACTIONAL VOLUMES OF TISSUES
VLC = 0.0366,    # Volume Liver as % Body Weight
VLUC = 0.005 ,    # Volume Lung as % Body Weight
VFC = 0.1  ,    # Volume Fat as % Body Weight
VRC = 0.04644 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.4  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0073 ,    # Volume Kidney as % Body Weight

#PARTITION COEFFICIENTS PARENT
PL = 1.57 ,     # Liver/Blood Partition Coefficient
PLU = 1.84 ,     # Lung/Blood Partition Coefficient
PF = 16.87 ,     # Fat/Blood Partition Coefficient
PS = 0.60  ,    # Slow/Blood Partition Coefficient
PR = 2.27 ,     # Rapid/Blood Partition Coefficient
PB = 7.35 ,     # Blood/Air Partition Coefficient
PK = 2.27 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
VMAXC = 9.48  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.05  ,  # Km for Oxidative Pathway:Liver
VMAXCLU = 0.0  ,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.25  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.15  ,    # Pseudo-first order clearance in lung (Km unidentifiable)
VMAXCKid = 0.02 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.07  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0    # Initial concentration (ppm)

)
```

```
#Male Rat paramters (Table 3 Yang et al. 2012)
#Metabolism is based on deterministic estimates with Nelder-Mead algorithem
#Male Fischer Rat

parms <-c(
BW = 0.25 ,      # Body weight
QPC = 21. ,      # Unscaled Alveolar Vent
QCC = 18. ,      # Unscaled Cardiac Output

#FRACTIONAL BLOOD FLOWS TO TISSUES
QLC = 0.183 ,    # Flow to Liver as % Cardiac Output
QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
QSC = 0.278  ,    # Flow to Slow as % Cardiac Output
QKC = 0.14  ,    # Flow to Kidney as % Cardiac Output

#FRACTIONAL VOLUMES OF TISSUES
VLC = 0.0366,    # Volume Liver as % Body Weight
VLUC = 0.005 ,    # Volume Lung as % Body Weight
VFC = 0.1  ,    # Volume Fat as % Body Weight
VRC = 0.04644 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.4  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0073 ,    # Volume Kidney as % Body Weight

#PARTITION COEFFICIENTS PARENT
PL = 1.57 ,     # Liver/Blood Partition Coefficient
PLU = 1.84 ,     # Lung/Blood Partition Coefficient
PF = 16.87 ,     # Fat/Blood Partition Coefficient
PS = 0.60  ,    # Slow/Blood Partition Coefficient
PR = 2.27 ,     # Rapid/Blood Partition Coefficient
PB = 7.35 ,     # Blood/Air Partition Coefficient
PK = 2.27 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
VMAXC = 7.997  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.0496  ,  # Km for Oxidative Pathway:Liver
VMAXCLU = 0.0  ,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.0885  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.1035  ,    # Pseudo-first order clearance in lung (Km unidentifiable)
VMAXCKid = 0.0133 , # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.0814  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0    # Initial concentration (ppm)

)
```

```
#Male rat paramters (Re-estimated CVL 2017)
#Metabolism is based on deterministic estimates from Nelder-Mead algorithm
#Km was fixed to average of male and female rat liver km
#Male Fischer Rat

parms <-c(
BW = 0.25 ,      # Body weight
QPC = 21. ,      # Unscaled Alveolar Vent
QCC = 18. ,      # Unscaled Cardiac Output

#FRACTIONAL BLOOD FLOWS TO TISSUES
QLC = 0.183 ,    # Flow to Liver as % Cardiac Output
QFC = 0.07  ,    # Flow to Fat as % Cardiac Output
QSC = 0.278  ,    # Flow to Slow as % Cardiac Output
QKC = 0.14  ,    # Flow to Kidney as % Cardiac Output

#FRACTIONAL VOLUMES OF TISSUES
VLC = 0.0366,    # Volume Liver as % Body Weight
VLUC = 0.005 ,    # Volume Lung as % Body Weight
VFC = 0.1  ,    # Volume Fat as % Body Weight
VRC = 0.04644 ,    # Volume Rapid Perfused as % Body Weight
VSC = 0.4  ,    # Volume Slow Perfused as % Body Weight
VKC = 0.0073 ,    # Volume Kidney as % Body Weight

#PARTITION COEFFICIENTS PARENT
PL = 1.57 ,     # Liver/Blood Partition Coefficient
PLU = 1.84 ,     # Lung/Blood Partition Coefficient
PF = 16.87 ,     # Fat/Blood Partition Coefficient
PS = 0.60  ,    # Slow/Blood Partition Coefficient
PR = 2.27 ,     # Rapid/Blood Partition Coefficient
PB = 7.35 ,     # Blood/Air Partition Coefficient
PK = 2.27 ,     # Kidney/Blood Partition Coefficient

#KINETIC CONSTANTS
MW = 88.5  , # Molecular weight (g/mol)
VMAXC = 8.9347  , # Scaled VMax for Oxidative Pathway:Liver
KM = 0.0611  ,  # Km for Oxidative Pathway:Liver
VMAXCLU = 0.0045  ,  # Scaled VMax for Oxidative Pathway:Lung
KMLU = 0.0611  ,   # Km for Oxidative Pathway:Lung
KFLUC = 0.0  ,   # Pseudo-first order clearance in lung (Km unidentifiable)
VMAXCKid = 0.0111, # Scaled VMax for Oxidative Pathway:Kidney
KMKD = 0.0611  ,  # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0    # Initial concentration (ppm)

)
```

Message

From: Harvey Clewell [HClewell@ramboll.com]
Sent: 2/27/2019 8:34:42 PM
To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]
CC: Robinan Gentry [rgentry@ramboll.com]; Sonja Sax [SSax@ramboll.com]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]
Subject: Re: Chloroprene PBPK model documentation

Thanks for the careful review, Paul. We'll make the corrections you identified.

With kind regards,

Harvey Clewell

On Feb 27, 2019, at 2:19 PM, Schlosser, Paul <Schlosser.Paul@epa.gov> wrote:

> Harvey, all,
>
> I've started going over some of the report, and checking to be sure parameters are set properly in my model files. My understanding is that the .model file has not changed, only some of the parameters, so I would only need to update those. I see that you've updated the mouse QCC using the ventilation-perfusion-ratio (VPR) from the Marino DCM model. I think this is a good choice, since the value is > 1 for rats and humans, and the result is between the VPR for those other two species.
>
> In the spreadsheet attached I've used highlights to identify where things have changed, or I find some small discrepancies.
>
> Yellow: values (and citations) that changed in the spreadsheet from what was sent last August, but are consistent between the two pdf files sent, and the PCs all match the separate spreadsheet you sent with those calculations. So these are fine as is; I'm just highlighting for the record, outcome of our QA.
>
> Orange (not avail as highlight color for Outlook): values in the spreadsheet that match those in the *_model_files_* pdf (R scripts), but are different from Table S-I in the 'Model Report' pdf. I think Table S-I just needs to be corrected.
>
> Green: Male mouse QSC and female mouse Vmaxc in the model files (R scripts) do not match what's in the Model Report, which does match the value that was in the 'Documentation' spreadsheet that I received last August. Since the Model Report and original Documentation spreadsheet did match, and male mouse QSC should match the female value, I think the R scripts should be corrected to match the values in the spreadsheet.
>
> Note (mentioned in an email last fall): in my model files I created "Mouse_phys.R" and "Rat_phys.R" scripts, which contain the physiological parameters and PCs for the respective species, since these do not differ between males and females. There are then separate male/female files for the metabolic parameters, but only those parameters. I prefer to keep this structure, easier to QA, hence I will be checking the values in my scripts against this spreadsheet, rather than copying in the ones in the pdf.
>
> Best regards,
> -Paul

From: Schlosser, Paul
Sent: Friday, February 22, 2019 3:09 PM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Sonja Sax <SSax@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: Chloroprene PBPK model documentation

Harvey,

Thanks for letting me know on the kg studies. I've been wanting to look at the report but am still playing catch-up after the furlough. A couple of other things are on a shorter time-line, but I'm hoping to get on to it next week.

-Paul

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Friday, February 22, 2019 11:56 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; Sonja Sax <SSax@ramboll.com>
Subject: Chloroprene PBPK model documentation

Hi Paul

Just an update on the status of the kg study. The water bath is expected to arrive at the laboratory next week, and the experiments will start as soon as they get it. Have you had a chance to look at the model report? Let me know if you have any suggestions.

With kind regards
Harvey Clewell
PhD, DABT, FATS
Principal Consultant
Ramboll Environment and Health Consulting
Research Triangle Park, NC 27709 USA
hclewell@ramboll.com
919-452-4279

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, February 5, 2019 8:15 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Sonja Sax <SSax@ramboll.com>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: Chloroprene PBPK model documentation

Hi Harvey,

OK, we also got these via Denka/EPA channels, sent Friday and I had a first glance yesterday, but wasn't sure what to think of them since there's still the 'kg' studies in progress. But it makes sense that the primary (in vivo) model

code wouldn't be impacted by those, just parameter values. So we could do more QA on the model files and review the report. However quantitative results may change some, even if the sensitivity analysis you did in the fall indicates it might not be much, depending on the impact of the kg experiments.

I am still trying to pick up the pieces after 4 works of furlough, and we're waiting to see when a full budget is passed, but I should be able to start reviewing the report next week. I scrolled through the model files and those look pretty straight-forward.

Best regards,
-Paul

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Monday, February 04, 2019 5:39 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; cvanlandingham@ramboll.com; Sonja Sax <SSax@ramboll.com>
Subject: Chloroprene PBPK model documentation

Hi Paul

I am sending you a report that we prepared for Denka describing the in vivo validation study performed at the Hamner and documenting the chloroprene PBPK modeling progress as of 1 February 2019. The report was submitted to the EPA's Office of Enterprise Information Programs on Friday in response to their request for any additional information related to Denka's Request for Correction of the 2010 Toxicological Review of Chloroprene. I have also attached the computer code (in R) for the model that was sent with the report. The model code has not changed, apart from updating some of the parameter values based on your previous recommendations. I will be using the report as the basis for the eventual publication on the in vivo study and PBPK model after we are able to incorporate the results of the kg study that you requested. I would appreciate any comments or suggestions you have on the report, whenever you have a chance to look at it, but there's no hurry. I'll be continuing to work on the manuscript as we move forward with the metabolism parameter re-estimation.

With kind regards
Harvey Clewell
PhD, DABT, FATS
Principal Consultant
Ramboll Environment and Health Consulting
Research Triangle Park, NC 27709 USA
hclewell@ramboll.com

<Chloroprene Documentation_02.27.19.xlsx>

Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/6/2018 1:45:39 PM
To: Jerry Campbell [JCampbell@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]; Harvey Clewell [HClewell@ramboll.com]
CC: Robinan Gentry [rgentry@ramboll.com]; Allison Franzen [AFranzen@ramboll.com]; Miyoung Yoon [myoon@toxstrategies.com]; Sonja Sax [SSax@ramboll.com]
Subject: RE: transmission of PBPK model for chloroprene

Well the .dll came through the first time. I was going to send my DropBox link…

Anyway, I had seen that the scripts were all there, but not those two in the zip/txt attachment. So we just have to rebuild it.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 06, 2018 9:40 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; cvanlandingham@ramboll.com; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I think it was the .o and/or .dll files that caused the hiccup. That was the problem we always had with emailing aclsX models.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 9:33 AM
To: Jerry Campbell <JCampbell@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

That worked!

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 06, 2018 9:30 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; cvanlandingham@ramboll.com; Harvey Clewell

<HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I was just getting to that option. See if this will work.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 9:26 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Try just changing the file-extension from .zip to .txt and sending as an attachment. I'm trying to unzip the thing from the sharepoint site and just getting a spinning wheel.

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:19 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Unfortunately, I believe that the restrictions are on your end not ours. We can all see the files no problem.

Cynthia

Cynthia Van Landingham
Senior Managing Consultant

D +1 (318) 3982091
M +1 (318) 6147920
cvanlandingham@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 8:18 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I tried to just download it. Does it have to be this complicated? We'll be sharing with everyone as part of our open and transparent process…

-Paul

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:13 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Paul,

Did you download the zip file to your hard drive and then open or did you open it on the OneDrive site? If you did not try this, selecting all the files and allowing OneDrive to produce one download zip may be best. The chloroprene_model.o_error.txt file is not in the zip we created so may be something that is being created due to the download process. Please read that file to find out if your IT security set-up is preventing files from being extracted.

Thanks, Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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M +1 (318) 6147920
cvanlandingham@ramboll.com

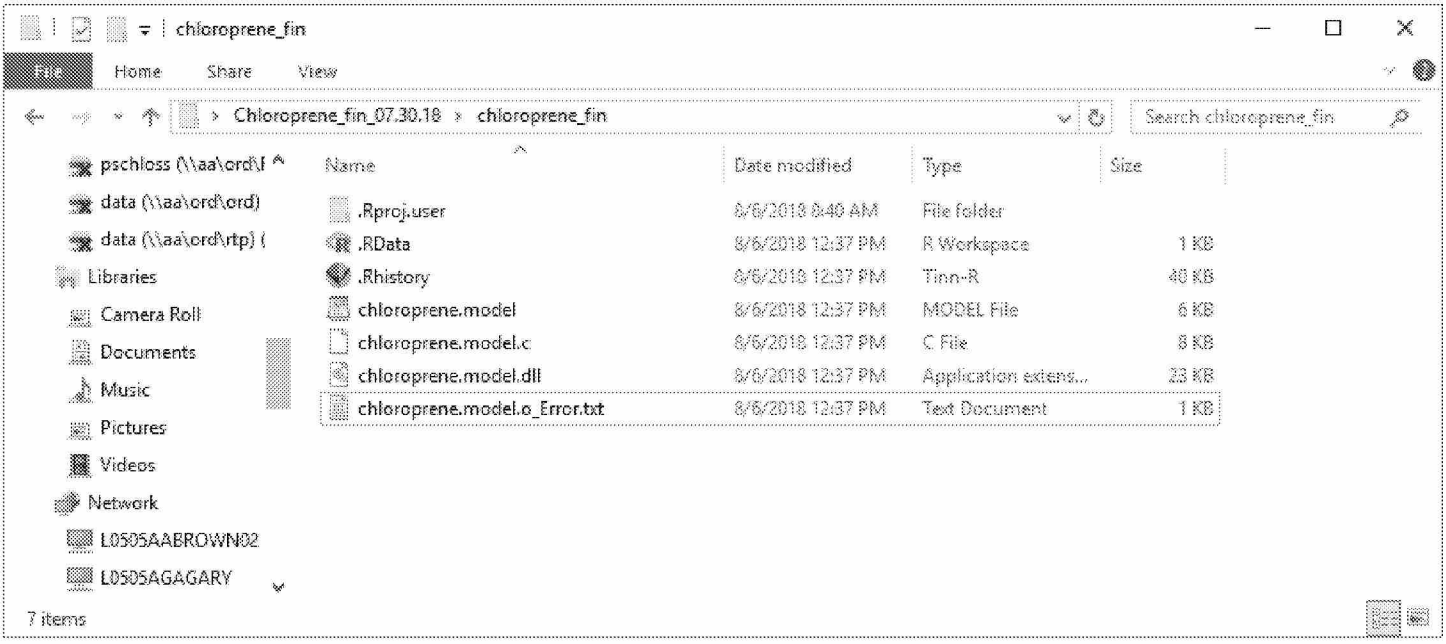
From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 7:53 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

PhD, DABT, FATS
Principal Consultant
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hclewell@ramboll.com

Connect with us

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Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/30/2018 12:43:07 PM
To: HIMMELSTEIN, MATTHEW W [Matthew.W.Himmelstein@dupont.com]
CC: Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Jerry Campbell [JCampbell@ramboll.com]; Harvey Clewell [HClewell@ramboll.com]
Subject: question about chloroprene in vitro experiments

Hi Matt,
Cc: Alan, Allen, Jerry, Harvey

I hope all is well.

I know this is going back a while… In the 2004 chloroprene in vitro PK paper it says that samples were taken every 12 min, but the data show them as more frequent.

Jerry thought that these were from running replicate vials with a fixed-interval auto-sampler, just starting the sampling at different times. That makes sense but I wanted to confirm with you, to be sure that the loss term in the model for the in vitro system was correct, counted the right number of samples.

Thanks,
-Paul

~~~~~~~~~~~~~~~~~~~~~~
Paul M. Schlosser
NCEA, U.S. EPA
M.D. B243-01
RTP, NC 27711
T: 919-541-4130
F: 919-685-3330
E: schlosser.paul@epa.gov
~~~~~~~~~~~~~~~~~~~~~~

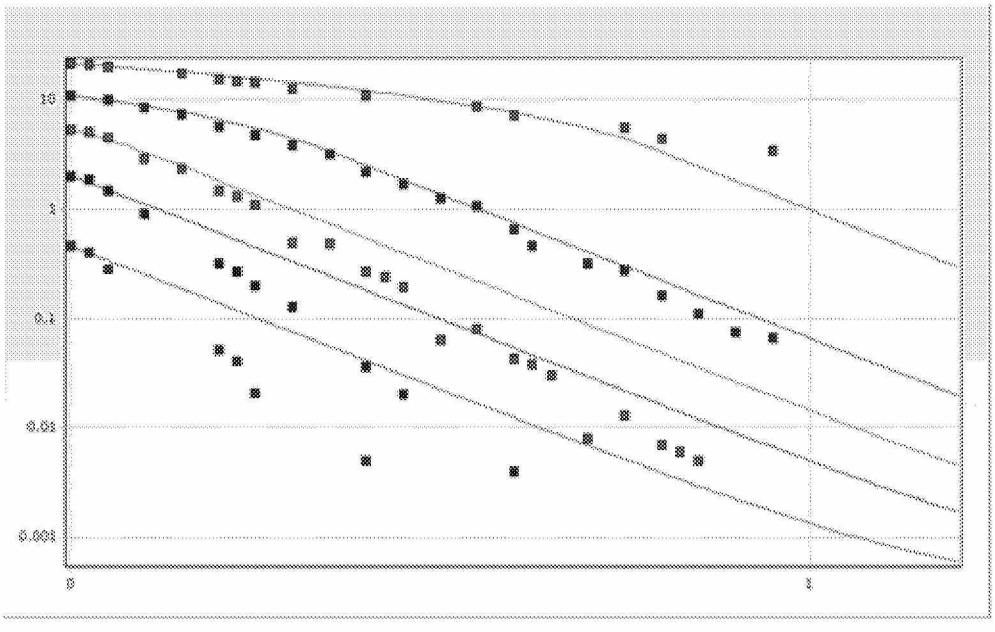
Message

From: Harvey Clewell [HClewell@ramboll.com]
Sent: 10/2/2018 7:26:46 PM
To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]
CC: Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Jerry Campbell [JCampbell@ramboll.com]; Robinan Gentry [rgentry@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]; Sonja Sax [SSax@ramboll.com]; HIMMELSTEIN, MATTHEW W [Matthew.W.Himmelstein@dupont.com]
Subject: RE: Chloroprene In Vitro model

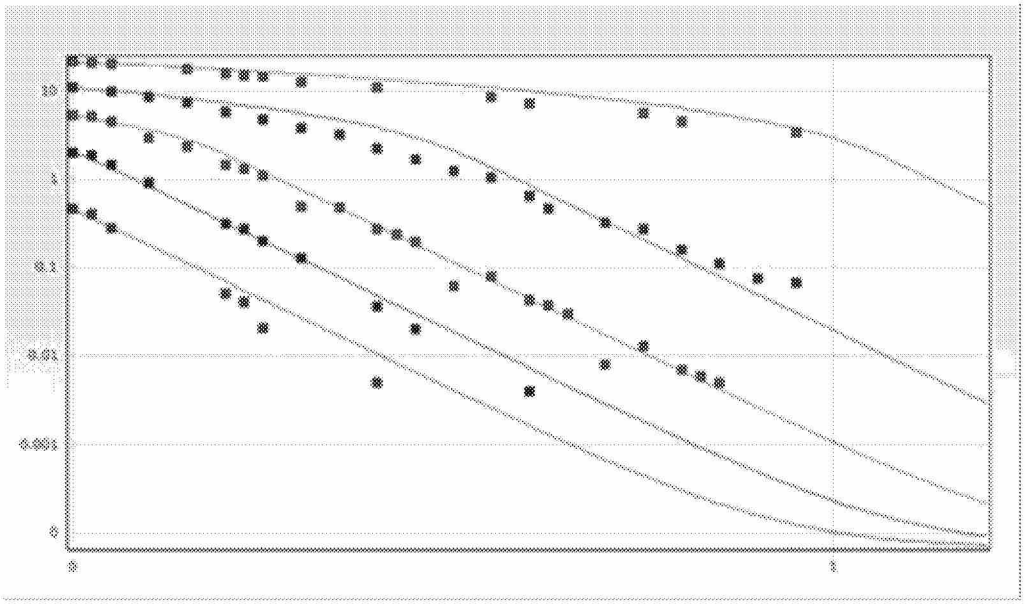
Hi Paul

We've performed an analysis to estimate the potential impact of the use of an equilibrium assumption in the estimation of the in vitro metabolism parameters. Based on this analysis I don't believe it is necessary to conduct new studies to determine a kg for chloroprene. The male mouse liver data are adequate to inform the value of this parameter. Moreover, I'm concerned that such a study would be difficult to perform since the research laboratories that used to conduct such studies with volatiles (WPAFB, CIIT, CSU, Hamner) are no longer available. Does NHEERL still have the capability to perform such a study?

We began, as you did, with the male mouse liver, since that's the strongest data (highest metabolism rates). Scaling the kg from your benzene study (0.434 mL/min= 0.026 L/h) by the ratio of the surface areas in the 4 mL vials you used vs. the 10 mL vials Matt used results in a kg = 0.0636 L/hr and kl = kg/P(liquid/air), which is too low to fit the rate of metabolism at low concentrations.



Next, we used the Nelder-Mead optimization to jointly estimate Vmax, Km, and kg with kl set equal to kg/PC. The resulting estimate of kg was 0.100 L/hr, about 50% higher than the value estimated by scaling your benzene data.



Using this kg, the liver microsome Vmax decreased from 0.26 (Yang) to 0.19 umol/hr/mg protein and the Km decreased from 1.36 to 0.0028 uM. This is again consistent with what you found.

In order to evaluate the potential effect of kg on model predictions we used the kg estimated from the male mouse liver data to re-estimate the metabolism parameters for the liver, lung and kidney in the female mouse. The resulting dose metrics for the female mouse lung are not affected by the use of kg.

Yang et al. 2012 Table 3 Estimated Metabaolic Point Est. Used

Female Mouse Initial Parms			
PPM	AMP	AMPLU	AMPK
12.3	0.60	0.42	0.0015
32	1.60	0.66	0.0022
80	4.04	0.86	0.0027

Benzene KG Adjusted for Vial Surface Area

Female Mouse Initial Parms			
PPM	AMP	AMPLU	AMPK
12.3	0.61	0.42	0.0016
32	1.61	0.67	0.0017
80	4.08	0.86	0.0019

KG Optimized to Male Mouse Liver In Vitro

Female Mouse Initial Parms			
PPM	AMP	AMPLU	AMPK
12.3	0.60	0.41	0.0016
32	1.60	0.66	0.0018
80	4.07	0.86	0.0019

In retrospect, it makes sense that kg doesn't affect the model predictions since the only tissue where metabolism is sufficiently rapid to make kg rate-limiting is the liver, but at the bioassay concentrations liver metabolism is blood-flow limited so decreasing km does not increase the rate of liver metabolism.

Harvey Clewell

PhD, DABT, FATS
Principal Consultant
1692720 - Tampa

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M +1 (919) 4524279
hclewell@ramboll.com

---

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Wednesday, September 19, 2018 2:14 PM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <jcampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>
Subject: RE: Chloroprene In Vitro model

I'm sending again, including John Vandenberg, Kris Thayer, and Tina Bahadori.

-Paul

From: Schlosser, Paul
Sent: Wednesday, September 19, 2018 1:39 PM
To: 'HIMMELSTEIN, MATTHEW W' <Matthew.W.Himmelstein@dupont.com>; 'Jerry Campbell' <JCampbell@ramboll.com>
Cc: 'Harvey Clewell' <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt, all,

I'm following up to see how things stand regarding the search for additional data. In a separate note Harvey said there should be a report (IISRP?) for the earlier in vitro studies, which it could help to have. Please send any that you have.

As it stands, we have mostly halted our QA review, as it strongly hinges on the equilibration assumption in the in vitro modeling. The code for the in vitro and in vivo models has checked out, issues resolved, and I think all other parameter discrepancies have been resolved – a few changes but none that should make a really large difference.

I realize it might take some time for files to be retrieved from archives and reviewed, but it's now been a couple of weeks since I provided the written details on what we are seeking. Can you tell us where things stand on your end?

The simulations I've run/provided show that the fits to the low concentration in vitro data depend significantly on the assumption that gas-liquid equilibration is not rate limiting, and the data are consistent with the possibility that it is a factor, requiring a fairly large revision in the estimated Km value(s). As is, my conclusion is that there is uncertainty due to the lack of data on the mass transfer rate, and there isn't an easy way that I can think of (or that we are likely to undertake ourselves) for estimating or bounding that uncertainty. The model results are too uncertain to use, given the data and assumptions.

If data are obtained (from archives or newly developed) that show that mass transfer is a factor, it will then be up to Denka/Ramboll to revise the in vitro parameter estimation accordingly, and propagate that into the in vivo model, before we would continue our QA.

As indicated in previous emails, our QA will also involve comparing model predictions to the nose-only in vivo PK data from 2004: the model should be able to fit with parameters adjusted in a way consistent with the hypothesis that there may be an effect of the exposure system on respiration, but this would not be exposure-concentration-dependent. That

will require creating model scripts to run these simulations and compare model outputs to the data. While we are prepared to do that work as part of our QA, provided that the mass transfer data become available, we are not planning to begin that work until those data are available and any necessary revisions of the in vitro modeling have been completed. Alternately, Ramboll colleagues could create the scripts in the meantime, which would speed up the QA.

Sincerely,
-Paul

~~~~~~~~~~~~~~~~~~~~~~

Paul M. Schlosser
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M.D. B243-01
RTP, NC 27711
T: 919-541-4130
F: 919-685-3330
E: schlosser.paul@epa.gov

From: Schlosser, Paul
Sent: Wednesday, September 05, 2018 12:06 PM
To: 'HIMMELSTEIN, MATTHEW W' <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

Sorry. I was also wondering at the volume being 1.6 mL bigger than advertised, it seemed like a large discrepancy.

A memo is attached, but here is what I've gotten from looking at the code in the appendix of the report you sent:

- Data to indicate that mass transfer resistance is not significant are still lacking.

- The sample volume (VINJ) for all the CP ***oxidation*** experiments in the 2004 paper should be ~ 400 uL, including male mouse and rat liver and lung data. But the code in the report uses 385.8 uL for male data and exactly 200 uL for male data. Is the higher accuracy for the rodent male and human data supported by some measurements?

- Assuming a similar accuracy, the vial volume (VVIAL) for all experiments described in the 2004 paper should be 0.0120 L. This value should be used for male mouse and rat liver and lung data. (We'll use 0.0116 L for the female mouse and rat data and the kidney data.)

Thanks,
-Paul
~~~~~~~~~~~~~~~~~~~~~~

Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/29/2018 7:52:27 PM
To: Jerry Campbell [JCampbell@ramboll.com]
CC: Harvey Clewell [HClewell@ramboll.com]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]
Subject: RE: Chloroprene In Vitro model

We can ask Matt and he might well remember. The difference between treating it as discrete events and a continuous loss with the same average rate is minimal, from when I tested my original cluge. (Treating it as continuous is kinder to the solver, though less realistic.) So if he confirms the scheme you describe (just different initial times), then either assuming continuous sampling or an average initial sample time with discrete events at a fixed interval after that should give equivalent results. The part of the script I sent that sets sampling times can be easily replaced with a fixed set of times.

That leaves the question of the mass transfer constant.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Wednesday, August 29, 2018 3:17 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>
Subject: RE: Chloroprene In Vitro model

In essence, there was only one sample scheme (every 0.2 hr or 12 min) but I think it may be more complicated than you have coded. It was an automated system – older version of the combi-pal autosampler. In the more highly sampled incubations (2004 paper in vitro paper), Matt reports that up to 5 vials were used to complete a time-course. So, while there was a mass of sample removed at each time, it wasn't linear throughout the whole run. He does state that samples were taken at 12 min intervals which coincides with the 1 vial system data in the female mouse and rat studies. The question is, can we assume that the 0.2 interval samples in the more highly sampled time-course is from a standardized staggered vial system:

Vial 1: 0, 0.2, 0.4, etc…
Vial 2: 0.05, 0.25, 0.45, etc…
Vial 3: 0.10, 0.30, 0.50, etc…
Vial 4: 0.15, 0.35, 0.55, etc…
Vial 5: ???

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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, August 29, 2018 2:25 PM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>;

Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: Chloroprene In Vitro model

Jerry, Harvey,
Cc: Alan, Allen

So I've rigged the code and male mouse liver script to read the sample times from the data file and use those for the "injection" decrement. That should make it easy to apply to other experiments (species/tissues). It also has the separate air/medium compartments. "SET10" gives an initial concentration just in the air phase (I used it to check that the simulations fairly match my old BZ model when I try to simulate that).

I now have it plotting for both variable and fixed Km cases, though the fixed Km value was also hand-adjusted for only the male mouse liver data set. That was partly so I could create an acslX plot definition file (.aps, attached) for the comparison.

The revised .csl, male mouse liver .m file, and .aps are attached. Handling the outputs of multiple lengths is clunky, but as much as I'm willing to do right now.

So the issue as I see it is that one needs to know the mass transfer rate between the gas phase and medium in order to correctly interpret the in vitro data. I had assumed that Matt had done those experiments, included the transfer term, what we learned from working with James Bond. The rate will depend on the surface area in the vial and rate of shaking in the incubator. The rate that I got is clearly too slow to be consistent with the data, but that doesn't mean it's not partially rate-limiting in these experiments. And I don't have a strong intuition for how much it might matter. But the impact will be largest when the rate of metabolism is highest.

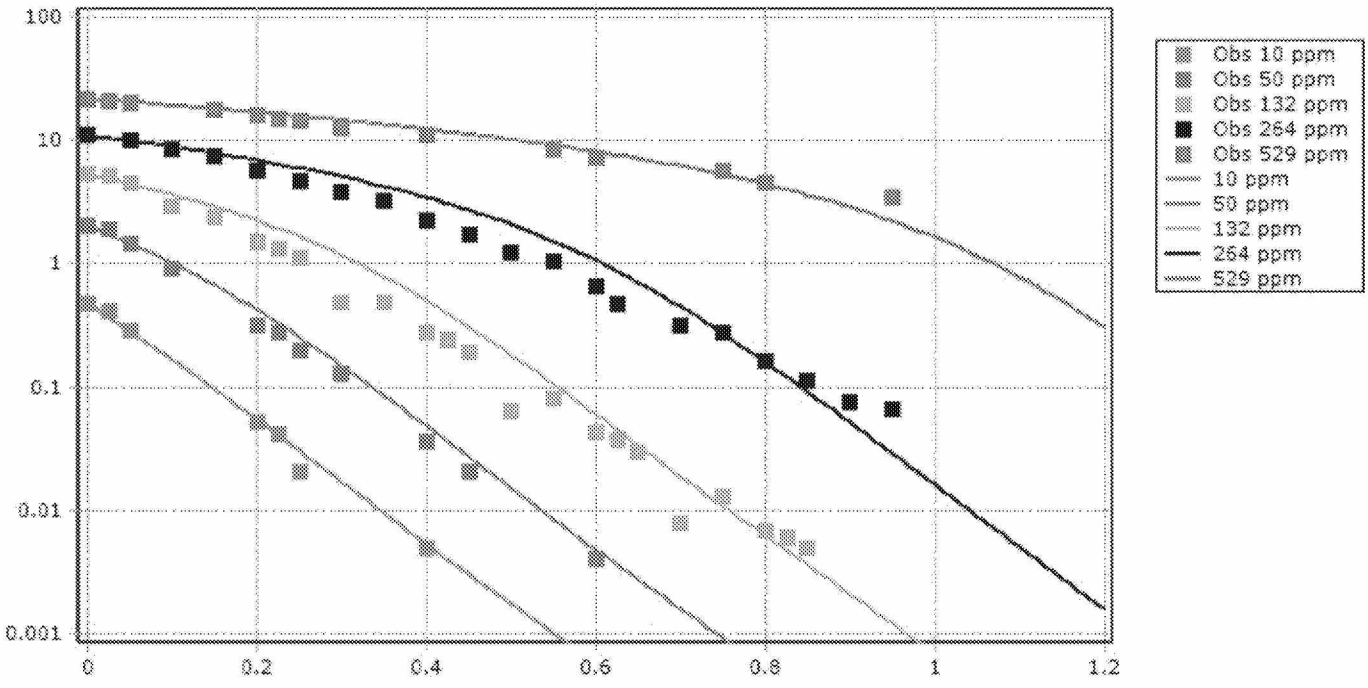
On the other hand, under-counting the sampling (male liver and lung data from Matt) will result in an over-estimate of metabolic rate for those experiments. That will have the largest relative impact when metabolism is slow. At least that just requires an adjustment of the code.

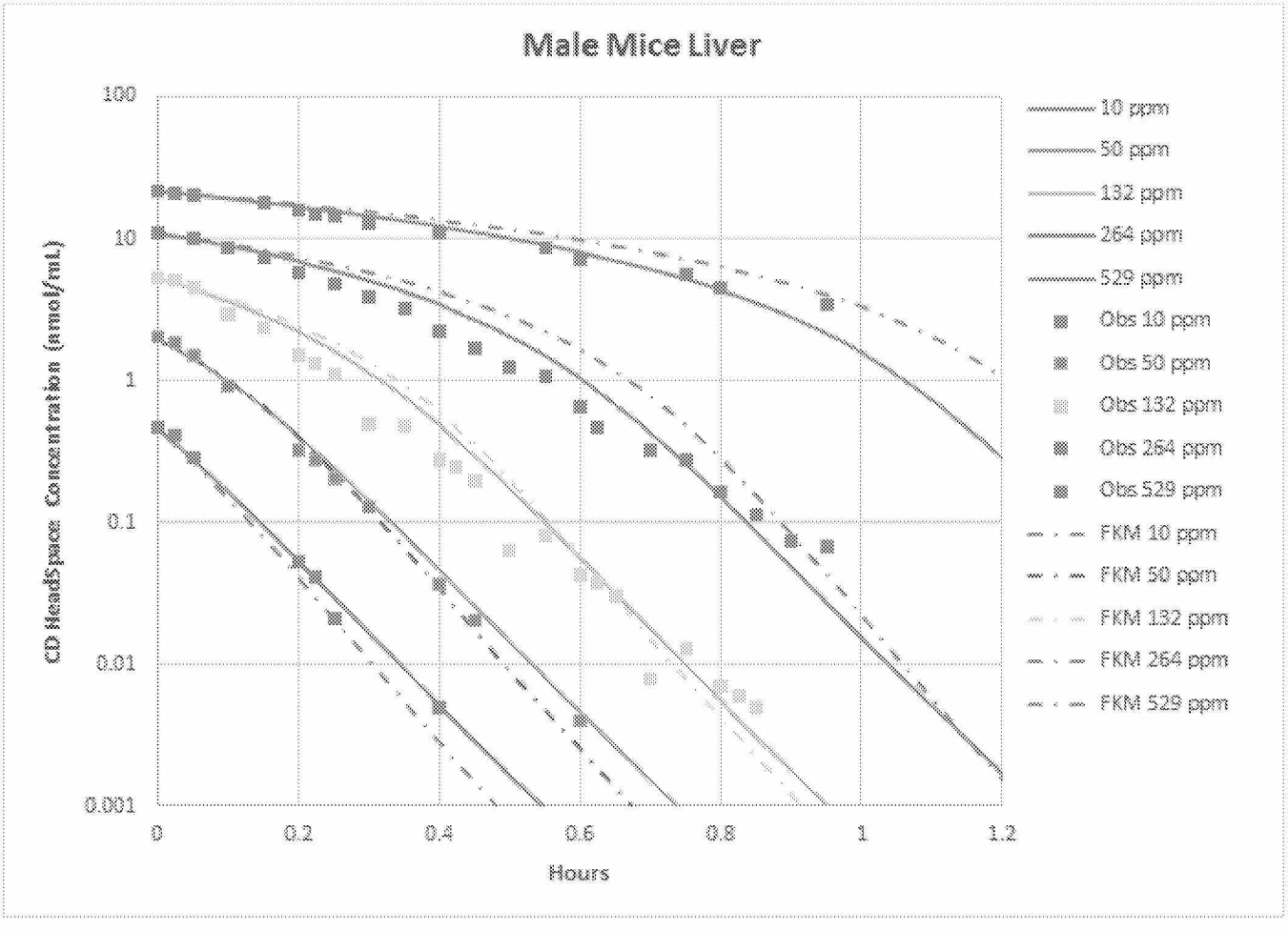
With regards,
-Paul

From: Schlosser, Paul
Sent: Tuesday, August 28, 2018 4:50 PM
To: 'Jerry Campbell' <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

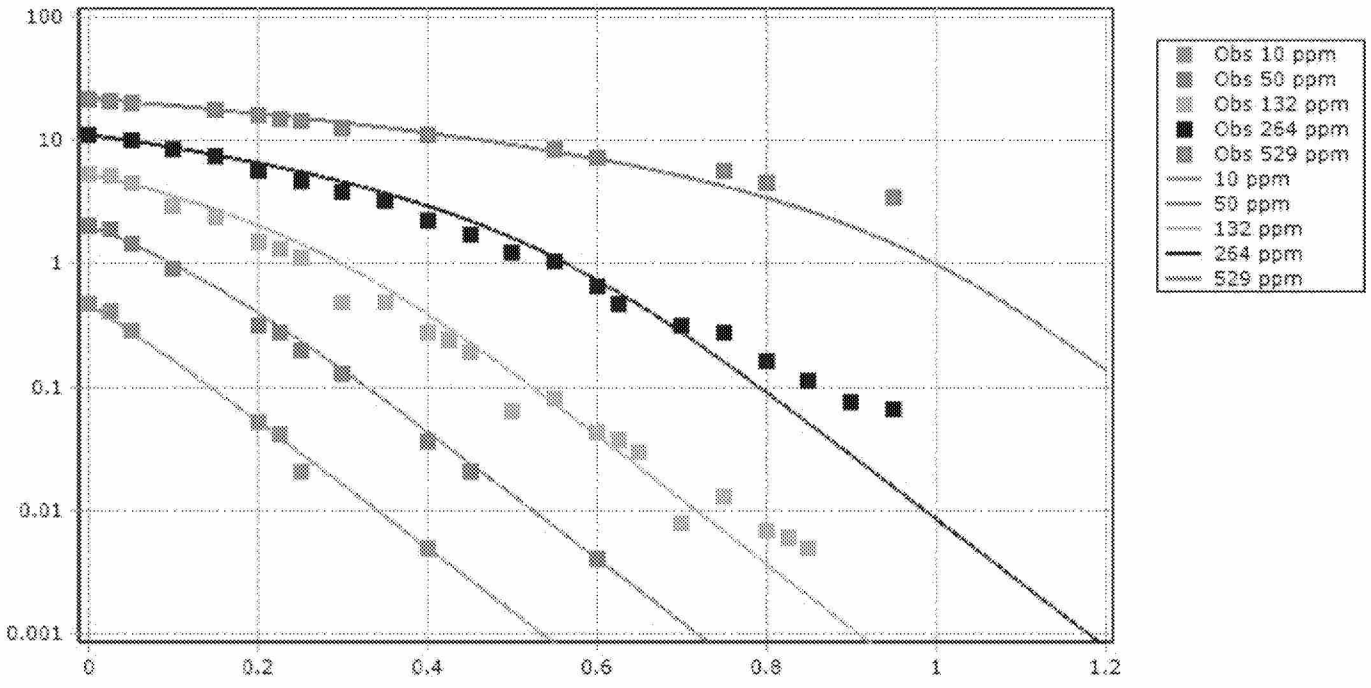
OK, so the first other thing I noticed was that the sampling time (TI) was set to 0.2 h, but clearly samples were taken at a higher frequency. To somewhat quickly get the model to allow for a variation in that, I can't use the procedural, as different sampling intervals changes the length of the output vector, so I can't combine the results in a single array. There's other ways around that, but my cluge was to treat sampling as a continuous loss at rate = VING/TI, where TI is calculated for each data set as TFINAL/NSAMPLE; i.e., the time of the final sample over the number of samples minus the one at time 0.

With the model changed to allow distribution between air and medium (so separate sub-compartments), TI fixed at 0.2 h, but an extremely high mass transfer coefficient (KGL) for air-medium, I get this, compared to the plot (for the Yang parameters) in the spreadsheet that Jerry sent (keep scrolling down):





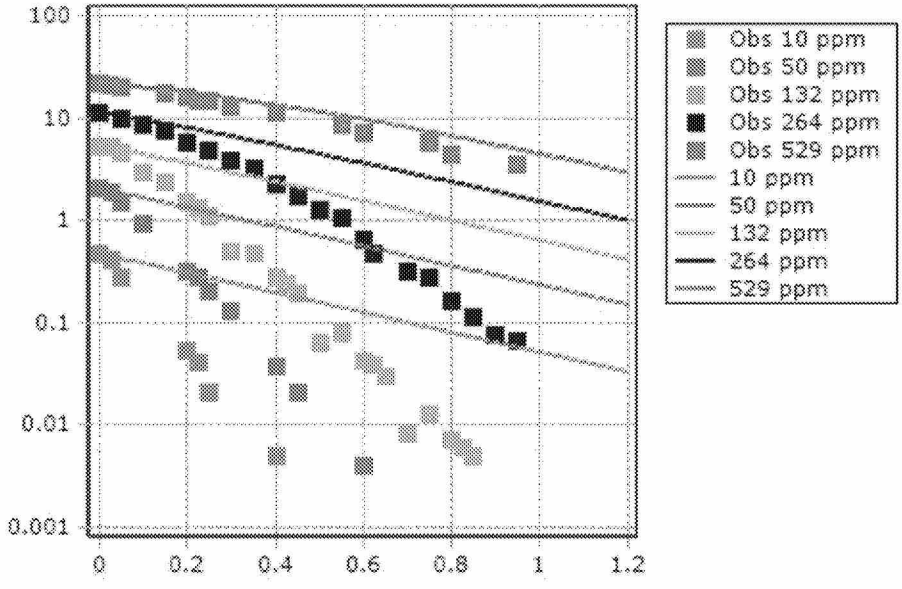
I'd say that's pretty good reproduction! Now, using the variable sampling time (TI), as described above:



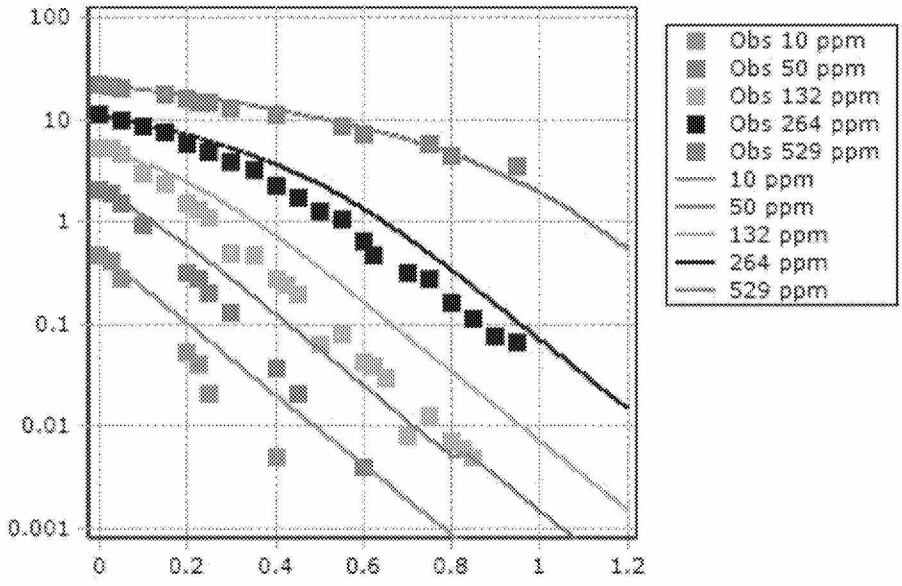
The difference isn't huge, but it's a difference…. For many of the experiments the interval is a fixed 0.2 h, but the male rat and mouse lung, and male rat lung are much more frequent. For the male mouse lung the metabolism is slower, which means the relative impact of this term will be greater.

Ideally the actual sample times should be used, with the scheduled procedural. That's a bit more programming but not terribly difficult. One will just need to deal with the fact that the output from each simulation will be a vector of a different length.

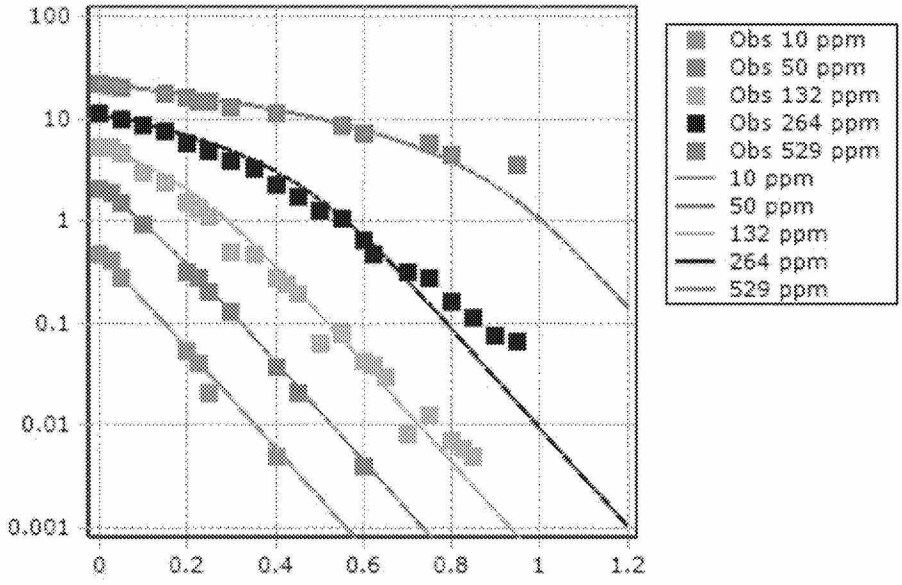
The bigger thing is the gas phase mass transfer. From my '93 benzene paper, the kg = 0.434 ml/min * 60 min/h * 0.001 L/ml = 0.026 L/h. Using that constant, so rate of movement from air to liquid (net) = 0.026*(Ca1 – Cm1/P1), I get:



Really bad, but then there may have been much less mixing in my smaller vials than Matt's, so I increased KGL by 10x, to 0.26:



I then reduced the Km from 1.36 to 0.8 (a bit of trial and error):



Based on this, I'd say that there's a very good chance that the gas-liquid mass transfer is a significant factor, and is likely to impact the estimation of Km (perhaps the goodness of fit of the fixed-Km model). The difficulty is that we need control incubation data to determine the correct value of KGL.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Tuesday, August 28, 2018 11:07 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Yes, it should be +ARLOSS. I must have hit the wrong key yesterday when I noticed it was missing from the equation.

Jerry Campbell
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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, August 28, 2018 8:42 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Thanks, Jerry. I've forwarded to Alan who is getting back to his evaluation of the primary model. I'm hoping we can get through the model code evaluation by the end of next week…

Well, I just looked at the .csl and see this:

```
!MASS BALANCE
  CHECK1 = A10 - (A1+A1M+A1I+ ARLUNGVK-ARLOSS)
```

But that should be +ARLOSS?

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 27, 2018 4:30 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>
Subject: Chloroprene In Vitro model

Paul,

I've uploaded a zip folder (INVITROMODEL AND GRAPHS.zip) with the full workspace for the in vitro model and Excel files with the figures. There is a spreadsheet with a list of the m-files and a short description. Let us know if something doesn't work or you have any questions.

Jerry Campbell

Managing Consultant

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Message

From: Cynthia Van Landingham [cvanlandingham@ramboll.com]
Sent: 8/6/2018 1:28:40 PM
To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]; Harvey Clewell [HClewell@ramboll.com]
CC: Robinan Gentry [rgentry@ramboll.com]; Allison Franzen [AFranzen@ramboll.com]; Jerry Campbell [JCampbell@ramboll.com]; Miyoung Yoon [myoon@toxstrategies.com]; Sonja Sax [SSax@ramboll.com]
Subject: RE: transmission of PBPK model for chloroprene

Please do not try to unzip from the sharepoint site. Wait 15 minutes and try to download the zip file again. We will remove the .o file and the .dll from the zip file which are the most likely to cause these problems and will upload the zip file again xo that should be ready in 15 minutes. Let us know if this does not work and we will find another way to get the files to you.

Thanks, Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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cvanlandingham@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 8:26 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Try just changing the file-extension from .zip to .txt and sending as an attachment. I'm trying to unzip the thing from the sharepoint site and just getting a spinning wheel.

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:19 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Unfortunately, I believe that the restrictions are on your end not ours. We can all see the files no problem.

Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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cvanlandingham@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 8:18 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

I tried to just download it. Does it have to be this complicated? We'll be sharing with everyone as part of our open and transparent process…

-Paul

From: Cynthia Van Landingham [mailto:cvanlandingham@ramboll.com]
Sent: Monday, August 06, 2018 9:13 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Paul,
Did you download the zip file to your hard drive and then open or did you open it on the OneDrive site? If you did not try this, selecting all the files and allowing OneDrive to produce one download zip may be best. The chloroprene_model.o_error.txt file is not in the zip we created so may be something that is being created due to the download process. Please read that file to find out if your IT security set-up is preventing files from being extracted.

Thanks, Cynthia

Cynthia Van Landingham
Senior Managing Consultant

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cvanlandingham@ramboll.com

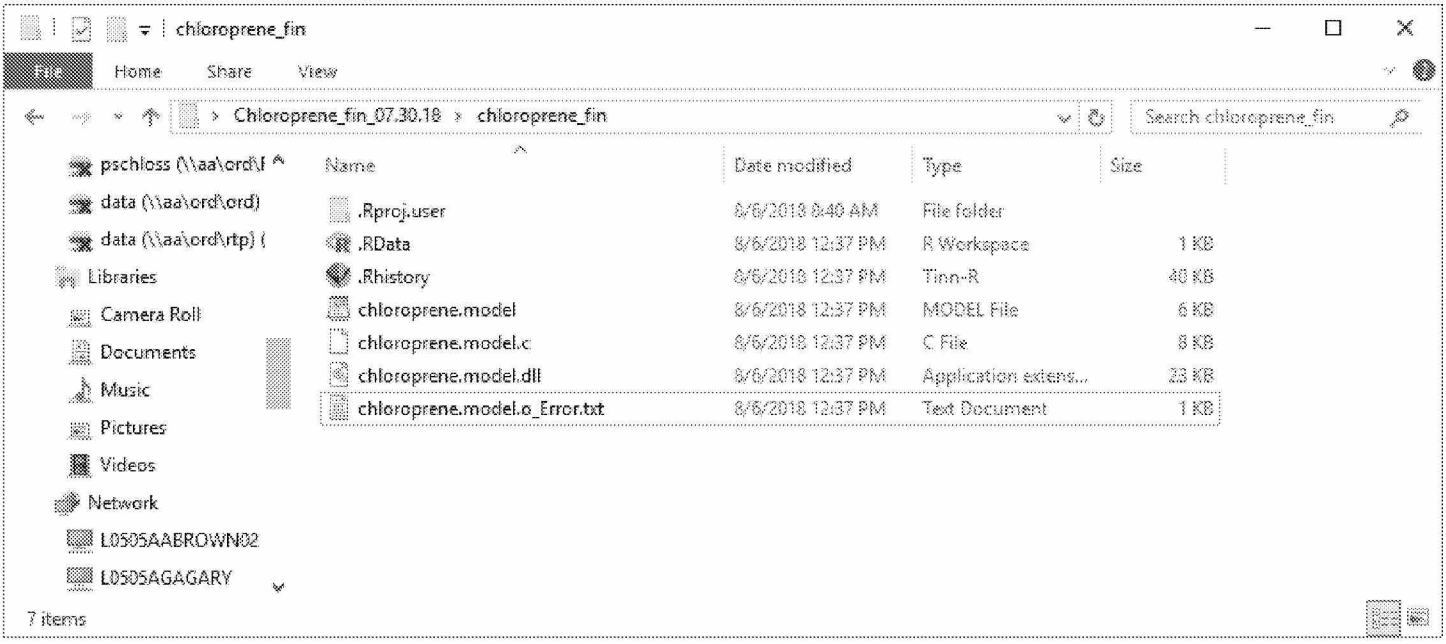
From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Monday, August 06, 2018 7:53 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Harvey,

I sent a separate email to Alison. Below is a screenshot of the model folder that I got. There are none of the scripts listed in the Excel 'documentation' file.

Once we have those, give us some time to look at it. Hopefully it's easy enough to figure out, but we can let you and Jerry know if we need a walk-through.

-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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